IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Shi, et al.
Serial No.	:	09/438,206
Group Art Unit	:	1617
Examiner	:	S. Hui
Filed	:	November 12, 1999
For	:	Methods and Compositions for Treating Mammalian Spinal Cord Injuries

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Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF DR. RICHARD BEN BORGENS

I, Richard B. Borgens, declare as follows:

1. I am a co-inventor of the above-referenced patent application.

2. I am a citizen of the United States of America.

3. In 1970, I received a B.S. Degree in Psychology, Anthopology minor from North Texas State University.

4. In 1973, I received a M.S. degree in Biology, Chemistry minor from North Texas State University. My thesis title was "Chronic Acceleration and Osteogenesis".

5. In 1977, I received a Ph.D. degree in Developmental Biology from Purdue University, West Lafayette, Indiana. My thesis title was "The Role of Bioelectricity in Amphibian Regeneration".

6. From 1977-1980, I was a National Paraplegia Foundation Fellow in the Department of Biology, Yale University, New Haven, Connecticut.

7. From 1980-81, I was Assistant Staff Scientist at Jackson Laboratory, Bar Harbor, Maine.

8. From 1981-82, I held the position of Associate Staff Scientist, at the Institute for Medical Research, Santa Clara Valley Medical Center, San Jose, California.

9. From 1982-84, I held the position of Assistant Professor, Department of Anatomy, School of Veterinary Medicine, Purdue University, West Lafayette, Indiana.

10. From 1984-1990, I held the position of Associate Professor, Department of Anatomy, School of Veterinary Medicine, Purdue University, West Lafayette, Indiana.

11. From 1987 until the present, I have held the position of Director, Center for Paralysis Research, School of Veterinary Medicine, Purdue University, West Lafayette, Indiana.

12. From 1990 until the present, I have held the position of Full Professor in the Department of Basic Medical Sciences, School of Veterinary Medicien, Purdue University, West Lafayette, Indiana.

13. From 2000 until the present, I have held the position of Full Professor in the Department of Biomedical Engineering, School of Engineering, Purdue University, West Lafayette, Indiana.

14. I have received numerous Special Honors and Award over the years, many of which are related to my work neuroscience, paralysis research and spinal cord injury.

15. I am a member of numerous scientific societies including the American Association for the Advancement of Science, Phi Zeta, Sigma Xi, Signma Tau Delta, Society of Developmental Biology, Society for Neuroscience, Society for Neurotrauma and Purdue University Neurosciences.

16. Over the years I have received numerous private and public grants to conduct research in the neuroscience area, and in particular, paralysis research.

17. I have authored/co-authored over 65 publications/articles in professional journals related to my research in neuroscience and primarily paralysis research and I have given numerous lectures/presentations in these areas.

16. My primary area of research is in neuroscience, with an emphasis on paralysis, spinal cord injury and the regeneration of neuronal tissue in paralyzed humans and other mammals.

17. I am familiar with the above-referenced patent application and I understand that the Examiner has rejected the claimed invention based upon the view that the prior art renders the invention obvious.

18. I have read the prior art namely, Bittner, Krause I, Krause II, Potter and Ishikawa and I do not believe that the present invention is obvious over teachings of the art. I understand that an invention is obvious when one of ordinary skill in the relevant art, believes that the claimed invention is obvious over the teachings which are set forth in the art.

19. The present invention is directed to a method of treating a mammalian patient having suffered an injury to its spinal cord, the method comprising contact the spinal cord as soon as is reasonably possible within a 24 hour period after the injury with an effective amount of a polyalkylene glycol compound as claimed, the method resulting in at least partial restoration of nerve function and an increased behavioral recovery after the spinal cord is treated.

20. None of the prior art teach the present method. For example, although Bittner, Krause I and Krause II describe a series of *in vitro* experiments using polyethylene glycol to reconnect or fuse severed axons primarily invertebrate axons, and in a few instances, with very limited success, vertebrate axons, none of these experiments was conducted in an *in vivo* setting. Moreover, the success rate of these *in vitro* experiments was somewhat mixed. There is nothing in the prior art references which suggests that polyalkylene glycols can be used *in vivo* to produce the restoration of nerve function and increased behavioral recovery exhibited by the present invention.

21. That *in vitro* experimentation is not predictive of *in vivo* results is clear, especially in neuroscience and spinal cord injury where a larger number of factors often enter the analysis in determining the result displayed. The present invention has exhibited unexpected activity in providing a treatment for spinal cord injury in mammalian patients, activity which is unexpected over the prior art experimentation.

22. There are simply too many factors which must be taken into account when attempting to predict results from *in vitro* experiments in animal models. For example, there are a number of limitations in the prior art *in vitro* experiments which make *in vivo* results impossible to predict.

23. For example, in the *in vitro* experiments which are described in the prior art, in the

chamber which is used for the experiments, there is no blood supply to the cord and it is not a factor in those experiments. The blood is completely washed out of the anaesthetized animal prior to the dissection of its spinal cord. In the first instance, the anesthesia provides somewhat of a protect effect of the axons which are removed and in the second instance there is no blood to complicate the process. In complete contrast, whole animals who have suffered a spinal cord injury generally suffer hemorrhagic injury. In the whole animal, there are issues of swelling and blood loss (ischemia) but also numerous biochemical consequences of blood chemicals such as heme and hemoglobin which catalyze various destructive chemical reactions which may lead to death. None of the complex interactions which exist in the live animal and are exacerbated during spinal cord injury occur during the *in vitro* experiments which are described in the art.

24. In the *in vitro* experiments of the prior art, the dissected spinal cord within the isolation chamber has had all of its nerve roots cut, and does not possess the brain which is left in the animal after dissection. Based upon the foregoing, there is simply no factual basis upon which one can predict the behavioral consequences of conduction changes in the isolation chamber.

25. In the *in vitro* experiments, many of the important physical and physiological processes such as oxygenation of the tissue, ionic concentrations of the perfusate, glucose concentration and temperature, among others, are under strict control, whereas in the animal model, virtually all of these factors are completely out of control following spinal trauma. In fact, virtually nothing is under control in the traumatized animal.

26. In the *in vitro* experiments of the prior art, the isolated spinal cord vetral white matter is only a fragment of the nervous system of the animals (primarily invertebrate) which are dissected. The neuronal fragment contains long expanses of single axons where one tests conduction. There are no synapses with other nerve cells in the tested "circuit", only axon

bundles which are kept alive under artificial conditions. In contrast, the present invention represents a treatment resulting in an increase in the *behavioral recovery* from spinal cord injury which is a function of the *entire neural circuit* involving millions of chemical synapses and the participation of innumerable other nerve and neural cells.

27. The dosage of drugs at an active site *in vivo* (related to turnover, metabolism, other pharmacokinetic parameters and their activity may not be entirely predicted without at least some other *in vitro* data, such as solubility, other parameters.

28. In the *in vitro* experiments, the health of the animal cannot be measured- indeed it is irrelevant to the experimental results and the determination of an end point defined as a recovery. In the spinal injured animal, every facet of the animal's state of health participates in the recovery process or the lack of recovery, facets which simply cannot be predicted *a priori* based upon *in vitro* data from limited experiments.

29. I am unaware of any contemporary publication which evidences the present invention by way of predictive *in vivo* experimentation.

30. Based upon the foregoing, it is my opinion that the present invention could not have been predicted from the teachings of the prior art and that based upon those teachings, the present invention represents an unexpected result and a clear advance in the art.

31. I further declare that all statements made herein of my own personal knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Aug 22, 2001

Richard Ben Borgens, Ph.D.

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DECLARATION OF DR. RICHARD BEN BORGENS

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: "Commissioner for Patents, Washington, D.C. 20231" on August 27, 2001.

R. Neil Sudol, Reg. 31,669